

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-942**

**CHEMISTRY REVIEW(S)**

DIVISION OF ANESTHETICS, CRITICAL CARE , AND  
ADDICTION DRUG  
PRODUCTS/HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-942

REVIEW # 3

DATE REVIEWED: 7/28/98

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	04-02-98	09-02-98	12-02-98
Amendment	04-03-98	06-03-98	
Amendment	30-04-98	04-05-98	
Amendment	16-07-98	17-07-98	

NAME & ADDRESS OF APPLICANT:

Hoffmann-La Roche, Inc.  
340 Kingsland Street  
Nutley, NJ 07110

DRUG PRODUCT NAME

Proprietary:

Versed (midazolam HCL) Syrup

Established:

Midazolam Hydrochloride  
RO 21-3981

Code Name/#:

Chem.Type/Ther.Class:

PHARMACOL. CATEGORY:

Anesthetic

DOSAGE FORM:

Syrup

STRENGTHS:

2mg/ml

ROUTE OF ADMINISTRATION:

Oral

DISPENSED:

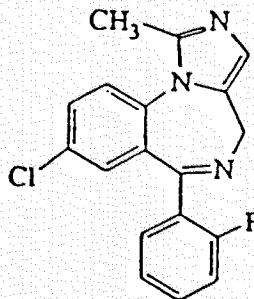
☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

MIDAZOLAM  
(8-Chloro-6-[2-fluorophenyl]-1-methyl-  
4H-imidazo-[1,5-a][1,4] benzodiazepine)

MOL. WT. 325.78

C<sub>16</sub>H<sub>13</sub>ClFN<sub>3</sub>



REMARKS:

In a teleconference with the applicant on July 14, 1998, we discussed the responses in their letters dated June 8 and 12, 1998. However, we still needed clarification to questions 5, 7, 11, 15, 16 and 17. This amendment of July 16, 1998 provides this additional information

CONCLUSIONS & RECOMMENDATIONS:

This application has been reviewed and the following consults have been resolved:

- Microbiology Review- completed and Satisfactory  
as of May 5, 1998
  - Environmental Assessment Report  
Requirement- Waviered 'as per Nancy Sager
  - Establishment Inspection Report
    - Hoffmann La Roche, Inc.  
Nutley, NJ- acceptable/May 15, 1998
    - Hoffmann La Roche, Inc.  
Basle, Switzerland - pending
  - Method Validation Packages sent:
    - Philadelphia District Laboratory  
July 7, 1998
    - San Juan District Laboratory  
July 8, 1998
- Results- Not Available

From a chemist viewpoint, the chemistry, manufacturing, and control issues have been resolved and the application can be approved pending a satisfactory recommendation from the Office of Compliance for the inspection of the Basle, Switzerland facilities.

/S/

7/28/98

Juanita Ross, Review Chemist

/S/

7/28/98

Albinus D Sa, Ph.D.  
Chemistry Team Leader

cc:  
Orig. NDA 20-942  
HFD-170/Division File  
HFD-170/JRoss  
HFD-170/DMorgan  
R/D Init. by:  
F/T by: JRoss  
filename: n20942

DIVISION OF ANESTHETICS, CRITICAL CARE , AND  
ADDICTION DRUG  
PRODUCTS/HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-942

REVIEW # 2

DATE REVIEWED:

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	04-02-98	09-02-98	12-02-98
Amendment	06-08-98	06-09-98	
Amendment	06-12-98	06-15-98	06-18-98

NAME & ADDRESS OF APPLICANT: Hoffmann-La Roche, Inc.  
340 Kingsland Street  
Nutley, NJ 07110

DRUG PRODUCT NAME

Proprietary: Versed (midazolam HCL) Syrup  
Established: Midazolam Hydrochloride  
Code Name/#: RO 21-3981  
Chem. Type/Ther. Class:

PHARMACOL. CATEGORY: Anesthetic

DOSAGE FORM: Syrup

STRENGTHS: 2mg/ml

ROUTE OF ADMINISTRATION: Oral

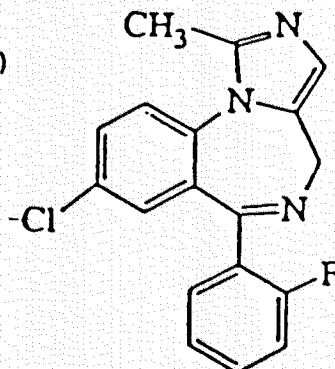
DISPENSED: ☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT

MIDAZOLAM  
(8-Chloro-6-(2-fluorophenyl)-1-methyl-  
4H-imidazo-[1,5-a][1,4] benzodiazepine)

MOL. WT. 325.78

C<sub>18</sub>H<sub>13</sub>ClFN<sub>3</sub>



REMARKS:

The firm has responded to our letter dated June 4, 1998.  
The responses have been reviewed and commented upon.  
There are still several issues that need to be resolved.

The following pages  
contain our comments concerning the applicants responses.

As has been stated before some of the following elements  
Have been resolved:

Microbiology Consult Report/HFD-160- Satisfactory

Environmental Assessment Report: Request for Waiver was granted

Establishment Inspection Report:

- Hoffmann La Roche, Inc. acceptable as per 5/15/98  
Nutley, N.J.
- Hoffmann La Roche, Inc. - synthesizes drug substance  
Basle, Switzerland Inspector is currently inspecting  
this facility

Method Validation Package: - has yet to be sent out, but will not  
effect the approval status

CONCLUSION AND RECOMMENDATIONS:

- From a chemist viewpoint, the application is approvable pending  
a satisfactory recommendation from the Office of Compliance for  
the inspection of the facilities

NDA 20-942  
Versed Syrup

3

/S/

Juanita Ross, M.Sc.  
Review Chemist

/S/

Albinus D'Sa, Ph.D.  
Chemistry Team Leader

cc:  
Orig. NDA 20-942  
HFD-170/Div. File  
HFD-170/JRoss  
HFD-170/DMorgan  
F/T by: JMRoss  
WP Files 20-942 rev.

DIVISION OF ANESTHETICS, CRITICAL CARE , AND  
ADDICTION DRUG  
PRODUCTS/HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-942

REVIEW # 1

DATE REVIEWED:

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	04-02-98	09-02-98	12-02-98
Amendment	04-03-98	06-03-98	
Amendment	30-04-98	04-05-98	

NAME & ADDRESS OF APPLICANT: Hoffmann-La Roche, Inc.  
340 Kingsland Street  
Nutley, NJ 07110

DRUG PRODUCT NAME

Proprietary:

Established:

Code Name/#:

Chem. Type/Ther. Class:

Versed (midazolam HCL) Syrup  
Midazolam Hydrochloride  
RO 21-3981

PHARMACOL. CATEGORY:

Anesthetic

DOSAGE FORM:

Syrup

STRENGTHS:

2mg/ml

ROUTE OF ADMINISTRATION:

Oral

DISPENSED:

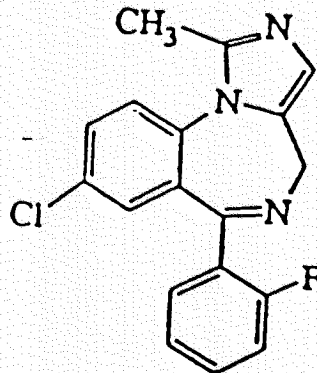
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CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

MIDAZOLAM  
(8-Chloro-6-(2-fluorophenyl)-1-methyl-  
4H-imidazo-[1,5-a][1,4] benzodiazepine)

MOL. WT. 325.78

C<sub>18</sub>H<sub>13</sub>ClFN<sub>3</sub>





SUPPORTING DOCUMENTS

Type/Number	Subject	Holder	Status	Compliance With:
NDA 18-654	New Drug Application for VERSED iNJECTION	Hoffmann-La Roche, Inc.	Satisfactory	Not Needed
DMF	Packaging Material Closures		Satisfactory	21 CFR Part 20
DMF	Packaging Material		Satisfactory	21 CFR 177.1520
DMF	Packaging Material		Satisfactory	21 CFR 177.1520
DMF	Dispenser-Resin		Satisfactory	21 CFR Part 880 USP 23 <1221>
DMF	Dispenser-		Satisfactory	21 CFR Part 820
DMF	Press-in Bottle Adapter		Satisfactory	21 CFR Part 820

NDA 20-94  
Versed Syrup

REMARKS:

VERSED Syrup, is a clear, red to purplish-red, cherry flavored syrup containing 2 mg/ml of midazolam hydrochloride, compendial excipients (USP/NF grade), flavors of acceptable GRAS Status, and a certified colorant.

Midazolam is a short- acting benzodiazepine central nervous system (CNS) depressant. Midazolam in solution is in equilibrium with the reactive open-ring form, Ro 21-6164. Since midazolam's solubility and equilibrium are pH dependent, the syrup is buffered to a pH range of 2.9 - 3.5.

The proposed packaging for the Versed Syrup is a 120 ml (4oz) amber glass bottle fitted with a non child-resistant cap with liner. Each bottle contains 118 ml of deliverable syrup and a press-in bottle adapter to aid in the removal of the syrup from the bottle with a 10 ml, graduated, oral dispenser. The Versed Syrup, 2 mg/ml is to be stored at 5°C - 25°C ( 41°F - 77°F) and their proposed expiration date is 18 months.

The application is still under review and outside consults are still pending, for instance:

- Microbiology Information sent to consultant/HFD-160 for review, on May 5, 1998. The consultant has responded in a review, dated May 28, 1998 and has concluded that the microbiology information is satisfactory and recommends approval of the application.
- Establishment Inspection request-
  - Hoffmann La Roche, Inc.- acceptable/5-15-98  
Nutley, NJ
  - Hoffmann La Roche, Inc.- pending  
Basle Switzerland
- Environmental Assessment Request for waiver- accepted/  
Nancy Sager
- Method Validation Package- to be sent out

**NDA 20-94**  
**Versed Syrup**

CONCLUSIONS & RECOMMENDATIONS:

This application has been reviewed and the substance of the review can be found in the The deficiencies in regard to  
chemistry, manufacturing, and controls have been cited and can be reviewed in  
However, the microbiology information is satisfactory; the environmental assessment requirement has been waived; and one of the two establishment manufacturing sites has been found acceptable. The inspection of the second site is still pending. Therefore, from a chemist viewpoint the application is approvable pending satisfactory responses to our information request letter dated June 4, 1998 and a satisfactory recommendation from the office of Compliance for the inspection of the facilities.

6/5/98

Juanita M. Ross, M.Sc.  
Review Chemist

6/5/98

Albinus D'Sa, Ph.D.  
Chemistry Team Leader

CC:

Orig. NDA 20-942  
HFD-170/Div File  
HFD-170/JRoss  
HFD-170/DMorgam  
F/T By: JMRoss